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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/646,449	08/22/2003	Menzo Havenga	2578-4489.1US	9509

24247 7590 09/15/2004

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EXAMINER	
MARVICH, MARIA	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 09/15/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/646,449	HAVENGA ET AL.	
	Examiner	Art Unit	
	Maria B Marvich, PhD	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *25 August 2003* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-21 are pending in the application.

Information Disclosure Statement

An IDS filed 8/25/03 has been identified and the documents considered. Documents listed as PCT reports have been considered but have been crossed off of the Form 1449 as PCT reports do not constitute documents under 37 CFR 1.98. The signed and initialed PTO Form 1449 has been mailed with this action.

Priority

Acknowledgment is made of applicant's claim for foreign priority based on an application filed in the European Patent Office on 7/8/1998. It is noted, however, that applicant has not filed a certified copy of the 98202297.2 application as required by 35 U.S.C. 119(b). Nor has a certified copy of the foreign application been found in applications 09/665472 or 09/348354.

Drawings

Figures 1, 4 and Figure 5 are objected to under 37 CFR 1.83(a) because they fail to show any details as described in the specification. Any structural detail that is essential for a proper understanding of the disclosed invention should be shown in the drawing. MPEP § 608.02(d). Specifically, the figures are bar graphs and the background is dark thus rendering the bars of the graph difficult to distinguish from the background. A proposed drawing correction or corrected

drawings are required in reply to the Office action to avoid abandonment of the application. The objection to the drawings will not be held in abeyance.

Double Patenting

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101, which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-5 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-5 of copending Application No. 10/381,088.

An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claims because the examined claim is either anticipated by, or would have been obvious over, the reference claims. Although the conflicting claims are not identical, they are not patentably distinct from each other because the cited claims of the instant invention are generic to all that is recited in claims 1-5 of copending Application No. 10/381,088. That is, the

cited claims of copending Application No. 10/381,088 anticipate and fall entirely within the scope of the rejected claims of the instant application. Specifically, copending Application No. 10/381,088 and the instant invention recite delivery of a heterologous nucleic acid to a dendritic cell. While the instant invention recites a method of delivering a heterologous nucleic acid comprising providing a recombinant adenoviral vector with a tropism for dendritic cells, copending Application No. 10/381,088 recites use of said recombinant adenoviral vector. Use of the vector anticipates a method for the use of delivering the vector.

Additionally, if a patent resulting from the instant claims was issued and transferred to an assignee different from the assignee holding the copending Application No. 10/381,088 then two different assignees would hold a patent to the claimed invention of copending Application No. 10/381,088,and thus improperly there would be possible harassment by multiple assignees.

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is vague and indefinite in that the metes and bounds of "includes a tropism for dendritic cells" are unclear. Does the vector encode tropism for dendritic cells or have associated with it a function that is intended to be "for the dendritic cells"?

Claim 2-4 and 8-21 are vague and indefinite in that the metes and bounds of "providing a recombinant adenoviral vector" are unclear. It is unclear if this vector is the same or distinct from the recombinant adenoviral vector of claim 1.

Claims 8-19 are vague and indefinite in that the metes and bounds of "based on" are unclear. It is unclear how closely related the recombinant adenoviral vector are to the first adenovirus and it is also unclear what the functional and structural relationship between the original adenovirus and those "based on" said adenovirus are. The metes and bounds of the claimed subject are unclear.

Claim 8 and 14 are vague and indefinite in that the metes and bounds of "the part of a non-native fiber protein" that is selected from fiber proteins are unclear. The claim recites "parts" of fiber proteins and therefore it is unclear how the parts can be selected from entire fiber proteins.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 2, 3, 8-21 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicants recite a genus of recombinant adenoviral vectors with at least partially reduced tropism for liver cells and with a genus of modifications that reduce replication of and immune responses to adenoviral vectors in a host compared to wild-type adenovirus.

Applicants recite a genus of parts of adenoviral capsid proteins or fiber proteins having a tropism for dendritic cells.

The written description requirement for genus claims may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with known or disclosed correlations between function and structure, or by a combination of such characteristics sufficient to show that the applicant was in possession of the claimed genus.

In the instant application, applicants teach that differences in the length of the fiber, knob sequence and other capsid proteins, such as the penton base, may determine the efficiency by which an adenovirus infects a certain target cell (page 6, paragraph 0013). Adenoviruses of serotype C, such as Ad2 or Ad5, transduce liver cells particularly well (see page 7, paragraph 0017) and in order to alter the tropism of ad5 vectors, applicants generated a library of chimeric adenovirus vectors "carrying the fiber molecule from alternative serotypes (serotypes 8, 9, 13, 16, 17, 32, 35, 45, 40-L and 51)". Chimeric fibers comprising fiber proteins of 11, 16, 35, 51 and 40-L exhibited efficient infection of immature dendritic cells (DCs) compared to Ad5 (page 14, paragraph 0053 and page 15, paragraph 0055).

Applicants do not disclose the tropism of the recombinant vectors for liver cells. Nor do applicants teach the immune response to the vectors. Applicants teach that E1A or E1B deleted

or mutated adenovirus vectors have reduced capabilities of replication and these vectors well known in the art and are preferred for gene therapy protocols. However, no other modifications to the vector are demonstrated such that replication of the vector is reduced as compared to wild type. Therefore, the instant specification lacks written disclosure of recombinant adenoviral vectors with reduced tropism for liver cells or reduced immune responses or with any modification such that replication is reduced. Given the large size and diversity potential recombinant adenovirus, the diversity of the recited physiological response such as replication, immune response and tropism, it must be considered that any functional fragment or mutation must be empirically determined. By disclosing ad5 comprising fiber proteins from ad11, 16, 40-L, 35 and 50, the applicants have not reduced to practice the claimed invention and the relationship between structure and function is unclear. In an unpredictable art, the disclosure of one example in one genus would not represent to the skilled artisan a representative number of species sufficient to show applicants were in possession of claimed genus.

As to "parts" of fiber proteins from a first or other adenoviral serotypes, applicants only disclose substitution of "fiber molecules". The fiber molecules absent evidence to the contrary appear to indicate the entire fiber protein. Therefore, applicant has not disclosed "parts" of the fiber. Therefore, there is no correlation between "at least parts" of fiber proteins and their ability to direct tropism for DCs or to reduce the tropism for liver cells. Given the diversity of parts of proteins and the inability to determine which will also possess the biologically activity, it is concluded that the invention must be empirically determined. In an unpredictable art, the disclosure of one species would not represent to the skilled artisan a representative number of species sufficient to show applicants were in possession of claimed genus.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-21 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for delivering heterologous nucleic acid to dendritic cells *in vitro*, does not reasonably provide enablement for delivering heterologous nucleic acid to dendritic cells *in vivo*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation (*United States v. Telectronics, Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is required is not based on a single factor but is rather a conclusion reached by weighing many factors (See *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter, 1986) and In *re Wands*, 8USPQ2d 1400 (Fed. Cir. 1988); these factors include the following:

1) Nature of invention. The invention recites a method for delivering a heterologous nucleic acid to dendritic cells using a recombinant adenovirus with tropism for DCs comprising fiber proteins and parts of fiber proteins from adenovirus serotypes 11, 16, 35, 40-L or 51. This invention requires a complex combination of molecular cloning in combination with viral and cell culture techniques to generate the recombinant adenovirus in combination with clinical techniques for administration of the particles to subjects.

2) Scope of the invention. The invention recites administration of the recombinant adenovirus to dendritic cells to deliver a nucleic acid of interest. The only recited *in vivo* uses are for gene therapy. The use of the recombinant adenovirus *in vivo* use exacerbates a complex invention.

3) Number of working examples and guidance. The specification teaches the development of immature dendritic cells in culture that express CF83-, $CD14^{low}$ or CD14+, HLA-DR+ phenotypes. These cells are infected with a library of chimeric adenovirus vectors "carrying the fiber molecule from alternative serotypes (serotypes 8, 9, 13, 16, 17, 32, 35, 45, 40-L and 51)". Chimeric fibers comprising fiber proteins of 11, 16, 35, 51 and 40-L exhibited efficient infection of immature dendritic cells (DCs) compared to Ad5 (page 14, paragraph 0053 and page 15, paragraph 0055). Applicants teach on page 2, paragraph 0002 that the invention is designed for gene therapy and some prospective applications are described on page 8, paragraph 0019-0020. However, the specification fails to demonstrate any examples or guidance for deliverance of nucleic acids to cells *in vivo*.

4) State of the art. There has been much interest in the development of viruses that transduce therapeutic genes into target tissues. However, the lack of established protocols and positive results has hampered the use of such inventions. Therefore, the art must be considered to be poorly developed.

5) Unpredictability of the art. Adenoviral vector use for gene therapy is hindered by the transient nature of the transgene expression coupled with host immune responses (Romano, Drug News and Perspectives, 2003, page 4). And as taught by Verma and Somia Nature p. 241; "Unfortunately for gene therapy, most of the human population will probably have antibodies to

adenovirus from previous infection with the naturally occurring virus" (Verma and Somia, Nature, 1997, p 241). And "although it may seem intuitive that a heightened immune response may be good in cancer gene therapy, it is less desirable on a practical scale because the immune response helps to eliminate the vector and to decrease the expression of the transduced gene (p. 4, column 2). Approaches to prolong transgene expression by multiple injections of adenovirus or to increase transgene expression cause have proven futile in the face of these host immune responses to the recombinant adenoviral vector (Kmiec, American Scientist, 1999, p 243).

The unpredictability of use of the instantly claimed invention in humans is accentuated by the lack of methods or processes disclosed in the specification. Many parameters must be addressed for *in vivo* use such as tumor cell selectivity in humans, lack of toxicity to normal tissues, and the effect of the antiviral immune response as well as doses to be administered, dose schedules etc. For example, what level of expression is necessary to achieve therapeutic affects without toxicity to normal cells that results from leaky expression of the viral gene required for replication? The method of delivery presents an obstacle for adenovirus use. "While reasonably accurate gene delivery can be achieved by direct inoculation of plasmids or recombinant viruses using a needle positioned in a tumour deposit. This strategy achieves a relatively low efficiency of gene delivery, which is confined to tumour cells immediately adjacent to the needle track. Plasmids or viral particles delivered in this way do not permeate freely through the interstitial fluid bathing the tumour." (Russell, European Journal of Cancer, 1994, p 1165).

6) Amount of Experimentation Required. The invention recites a method for delivering a heterologous nucleic acid to dendritic cells using a recombinant adenovirus with tropism for DCs. In view of the unpredictability of the art of delivering recombinant adenovirus

in vivo, the lack of guidance in the instant specification and the poorly developed state of the art: undue experimentation would be required to practice the claimed methods with reasonable expectation of success, absent a specific and detailed description in the specification. The level of skill in the art covering this invention was high at the time of invention; however, given the unpredictability of the art, the poorly developed state of the art, the lack of working examples and the lack of guidance provided by applicants, the skilled artisan would have to have conducted undue experimentation to practice the claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1 and 20 are rejected under 35 U.S.C. 102(e) as being anticipated by O'Riordan et al (US 6,287,857 B1; see entire document).

O'Riordan et al teach the development of vectors such as adenoviral vectors for transfecting target cell comprising a bifunctional complex for linking the vector to the target cell (see e.g. column 32, line 64-67, figure 9 and abstract). Target cells include dendritic cells (see e.g. figure 6 and column 29, line 9-27). Replication incompetent vectors for delivery are contemplated (see e.g. column 4, line 13-27).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 3-10, 12-17, 19 and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over O'Riordan et al (US 6,287,857 B1; see entire document) in view of Crystal et al (US 6,127,525; see entire document).

Applicants claim a method of delivering a heterologous nucleic acid to a dendritic cell in using a recombinant adenovirus in which parts of the fiber protein are substituted with parts of fiber proteins from adenovirus serotypes 11, 16, 35 and 40L.

The teachings of O'Riordan et al are above except: O'Riordan et al do not teach that the recombinant adenovirus comprises parts of fiber proteins from adenovirus serotypes 11, 16, 35, and 40L.

Crystal et al teach recombinant adenovirus comprising chimeric adenovirus coat proteins. The chimeric coat proteins include parts of proteins from ad5 and ad11 or ad16 or ad40 or ad35. The recombinant adenoviruses have a reduced ability to be recognized by a neutralizing antibody and altered tropism for new cell types (see e.g. abstract and column 4, line 32-42).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the recombinant adenovirus taught by O'Riordan et al with the recombinant adenovirus comprising chimeric coat proteins with fiber proteins from 1d11, ad 16, ad35 and ad40 as taught by Crystal et al because O'Riordan et al teach that it is within the

ordinary skill of the art to generate recombinant adenovirus with tropism for dendritic cells and because Crystal et al teach that it is within the ordinary skill of the art to use recombinant adenovirus with fibers from ad11, ad16, ad40 or ad35 for altered tropism. One would have been motivated to do so in order to receive the expected benefit of altered tropism of the recombinant adenovirus as well as decreased immunogenic response to the adenovirus. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria B Marvich, PhD whose telephone number is (571)-272-0774. The examiner can normally be reached on M-F (6:30-3:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, PhD can be reached on (571)-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR

system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Maria B Marvich, PhD
Examiner
Art Unit 1636

August 25, 2004

GERRY LEFFERS
PRIMARY EXAMINER